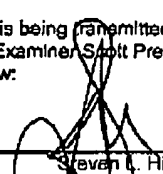


CERTIFICATE OF FACSIMILE TRANSMISSION 37 C.F.R. § 1.8	
I hereby certify that this correspondence is being transmitted to: Commissioner for Patents, Washington, D.C. 20231, Attn: Examiner Scott Priebe, GAU 1632, facsimile number (703) 746-3131 on the date below:	
September 19, 2003 Date	 Steven T. Highlander

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:  
Dennis E. HALLAHAN *et al.*

Serial No.: 08/540,343

Filed: October 6, 1995

For: METHODS AND COMPOSITIONS FOR  
VIRAL ENHANCEMENT OF CELL  
KILLING

Group Art Unit: 1632

Examiner: S. Priebe

Atty. Dkt. No.: ARCD:194/SLH

SUPPLEMENTAL INVENTORS' DECLARATION UNDER 37 C.F.R. §1.131

Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

We, the undersigned, do declare that:

1. We are citizens of the United States and named inventors on the above-captioned application.
2. A combination herpesvirus-radiation treatment of human tumor cells was performed in the United States country before June 23, 1994. Attached to this declaration is an invention disclosure prepared and signed by two of the inventors that is dated prior to June 23, 1994 (date

having been redacted). Therein, a statement is made to the effect of "HSV-1 mutants with  $\gamma$ 34.5 deleted are inoculated into human tumors and irradiated. The combination of virus and radiation is more cytotoxic than either agent alone." Though stated in the present tense, the statement reflects experiments that had been, in fact, performed.

3. To provide additional evidence that excerpted statement from the invention disclosure describes actual experiments performed by the inventors, we also attach to this declaration notebook pages describing some of the experiments discussed in the invention disclosure. The notebook pages illustrate experiments involving infection of human tumor cells with a  $\gamma$ -34.5-deleted HSV-1 strain, followed by radiation treatment of these cells. Surprisingly, no cancer cell colonies were observed with the combined HSV-1/radiation treatment, which was an improvement over either treatment alone. The experiments were performed in the United States prior to June 23, 1994.

4. We hereby declare that all statements made herein of our own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the referenced patent application or any patent issued thereon.

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Date

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Dr. Ralph Weichselbaum

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Date

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Dr. Dennis Hallahan

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Date

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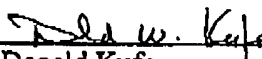
Dr. Gregory Sibley

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Date

9/6/03

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Dr. Donald Kufe

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Date

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Dr. Bernard Roizman

4. We hereby declare that all statements made herein of our own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the referenced patent application or any patent issued thereon.

\_\_\_\_\_  
Date

\_\_\_\_\_  
Date

9/9/3

\_\_\_\_\_  
Dr. Ralph Weichselbaum

\_\_\_\_\_  
Dr. Dennis Hallahan

*Dennis Hallahan*

\_\_\_\_\_  
Date

\_\_\_\_\_  
Dr. Gregory Sibley

\_\_\_\_\_  
Date

\_\_\_\_\_  
Dr. Donald Kufe

\_\_\_\_\_  
Date

\_\_\_\_\_  
Dr. Bernard Roizman

Received 09/16/2003 17:06 in 01:18 on line (5) for SH01973 printed 09/16/2003 17:09 \* Pg 4/4  
SEP. 16. 2003 4:57PM SIBLEY ONCOLOGY CT NO.571 P.4

4. We hereby declare that all statements made herein of our own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the referenced patent application or any patent issued thereon.

\_\_\_\_\_  
Date

\_\_\_\_\_  
Dr. Ralph Weichselbaum

\_\_\_\_\_  
Date

\_\_\_\_\_  
Dr. Dennis Hallahan

9/8/03  
\_\_\_\_\_  
Date

  
\_\_\_\_\_  
Dr. Gregory Sibley

\_\_\_\_\_  
Date

\_\_\_\_\_  
Dr. Donald Kufe

\_\_\_\_\_  
Date

\_\_\_\_\_  
Dr. Bernard Roizman

Received 09/18/2003 13:51 in 00:42 on line [6] for SH01973 printed 09/18/2003 13:55 \* Pg 2/2

4. We hereby declare that all statements made herein of our own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the referenced patent application or any patent issued thereon.

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Date

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Dr. Ralph Weichselbaum

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Date

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Dr. Dennis Hallahan

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Date

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Dr. Gregory Sibley

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Date

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Dr. Donald Kufe

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Date

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Sept 18 2003

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Dr. Bernard Roizman

4. We hereby declare that all statements made herein of our own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the referenced patent application or any patent issued thereon.

9/17/03  
\_\_\_\_\_  
Date

  
\_\_\_\_\_  
Dr. Ralph Weichselbaum

\_\_\_\_\_  
Date

\_\_\_\_\_  
Dr. Dennis Hallahan

\_\_\_\_\_  
Date

\_\_\_\_\_  
Dr. Gregory Sibley

\_\_\_\_\_  
Date

\_\_\_\_\_  
Dr. Donald Kufe

\_\_\_\_\_  
Date


\_\_\_\_\_  
Dr. Bernard Roizman

DRAFT

ARCH Project Manager		University of Chicago		UCHI # 499
		Confidential Invention Disclosure		Please print or type.
1. TITLE OF INVENTION/SOFTWARE <i>Enhancement of radiation killing with the viruses</i>				
2. INVENTOR(S)/Title*      Citizenship      Dept./Campus Address      Telephone #				
<i>Dennis Hallahan, MD</i>		<i>US</i>	<i>Radiation Onc</i>	<i>26819</i>
<i>Ralph Weichselbaum, MD</i>		<i>US</i>	<i>Radiation Onc</i>	<i>26819</i>
<i>Bernard Reizman</i>			<i>Virology</i>	<i>21898</i>
* Please attach curriculum vitae				
3. DESCRIPTION OF INVENTION - Attach any additional information or background documentation. <i>HSV-1 mutants with 834.5 deleted are inoculated into human tumors and irradiated. The combination of virus and radiation is more cytotoxic than either agent alone.</i>				
4. DISCLOSURE RECORD	DATE	REFERENCES & COMMENTS Use separate sheet if necessary or attach copy.		
A. First oral presentation of invention at seminars, meetings, conferences, etc.	<i>none</i>			
B. First publication, e.g. posters, articles, abstracts, seminars	<i>none</i>			
C. First successful demonstration, if any (reduction to practice)		<i>Lab notebook</i>		
D. Other Publications to Date				
E. Anticipated Publications	<i>, , ,</i>			

(over)



<b>5. RESEARCH SUPPORT</b>											
<p>A. Was the invention/discovery made in connection with any sponsored research? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <table style="width: 100%; border: none;"> <tr> <td style="width: 33%; text-align: center;">Sponsor</td> <td style="width: 33%; text-align: center;">Contract/Grant #</td> <td style="width: 33%; text-align: center;">Amount/Percent</td> </tr> </table>				Sponsor	Contract/Grant #	Amount/Percent					
Sponsor	Contract/Grant #	Amount/Percent									
<p>B. If no contract or grant, was there use of University funds or facilities? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p>											
<b>6. BACKGROUND RESEARCH AND PRIOR ART</b> related to your invention: (See attached instructions)											
<p><input type="checkbox"/> No relevant prior art exists</p> <p><input type="checkbox"/> See attached description</p> <p><input checked="" type="checkbox"/> See attached publications or references <i>Adams Associated Viro's</i></p>											
<b>7. RECORDS</b> to substantiate your invention's history includes: (See attached instructions)											
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <input checked="" type="checkbox"/> Laboratory notes and records  <input type="checkbox"/> Witnessed and Dated?  <input type="checkbox"/> Financial documents  <input type="checkbox"/> Dated photographs </td> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Idea only  <input type="checkbox"/> Rough sketches/diagrams  <input type="checkbox"/> Finished, working drawings  <input type="checkbox"/> Other </td> </tr> </table>				<input checked="" type="checkbox"/> Laboratory notes and records <input type="checkbox"/> Witnessed and Dated? <input type="checkbox"/> Financial documents <input type="checkbox"/> Dated photographs	<input type="checkbox"/> Idea only <input type="checkbox"/> Rough sketches/diagrams <input type="checkbox"/> Finished, working drawings <input type="checkbox"/> Other						
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<b>8. TESTING</b> which has already been conducted includes:											
<p><input type="checkbox"/> None</p> <p><input checked="" type="checkbox"/> Functional testing of prototype to determine if it operates as intended</p> <p><input type="checkbox"/> Market testing of invention</p>											
<b>9. POTENTIAL LICENSEES</b>											
<p>A. Please list any companies which you think may be interested in your invention.</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Company</td> <td style="width: 33%;">Address</td> <td style="width: 33%;">Contact Person</td> <td style="width: 33%;">Telephone #</td> </tr> <tr> <td><i>Gen Yec</i></td> <td></td> <td></td> <td></td> </tr> </table>				Company	Address	Contact Person	Telephone #	<i>Gen Yec</i>			
Company	Address	Contact Person	Telephone #								
<i>Gen Yec</i>											
<b>10. TECHNICAL/MARKETING CONTACTS</b> (See attached instructions)											
Company	Address	Contact Person	Telephone #								
<b>11. SUBMITTED BY:</b> <i>Dennis Hollahan</i> Inventor's Signature _____ Date _____  Co-Inventor's Signature _____ Date _____  Co-Inventor's Signature _____ Date _____		<b>DISCLOSED TO AND UNDERSTOOD BY:</b> Witness' Signature _____ Date _____ Witness' printed or typed name _____ <b>REVIEWED BY:</b> Department Head _____ Date _____ Printed or typed name _____									

**THE UNIVERSITY OF CHICAGO  
CONFIDENTIAL INVENTION DISCLOSURE DOCUMENT**

**GUIDE FOR PREPARATION OF INVENTION DISCLOSURE**

Completing this confidential document is the first step toward protecting and commercializing your invention. After the invention disclosure is completed, it will be recorded and filed at the Technology Center. A copy will be sent to ARCH Development Corporation (ARCH). ARCH is a non-profits affiliate of the University, and is responsible for patents, licenses and the formation of new companies at the University and Argonne National Laboratory.

The following instructions refer to the correspondingly numbered sections on the attached document.

1. Disclose only one invention. Use a separate form for each invention.
2. In naming co-inventors and co-authors, be careful to include all of those who had a creative role in the invention or software development. However, do not add names to recognize others who were not inventors or authors. Either the omission of a co-inventor/author or the inclusion of a non-inventor/author could invalidate a patent or impair a copyright.
3. Use simple language to describe your invention and define technical terms.
4. If you have published or presented this invention previously, please submit copies.
  - (A) Oral presentation or publication to third parties more than one year before filing a U.S. patent application will preclude obtaining U.S. patent protection. Publication or oral presentation to third parties prior to the filing of a patent application will preclude foreign patenting.
  - (B) The term "first publication" means the first time any member of the general public (without restriction of confidentiality) would have been able to legally gain access to your written or printed detailed description of the invention. (For example, the date when a journal containing your description is first mailed to the public.)
  - (C) Reduction to practice occurs when an invention has been (1) embodied in some physical form which is (2) used to demonstrate its workability.
5.
  - (A) Give the applicable contract or grant number(s) if the invention was made in connection with any sponsored research. Indicate Principal Investigators by the notation P.I.
  - (B) Significant use of University-administered resources—whether funds or facilities—will normally give rise to University ownership rights in an invention. (For more details, you may request a copy of the University's Statute 20 Patents and Software policy from the Technology Center.)
6. Please provide a general description of the background research and pertinent prior work done in the field related to your invention. If possible, list five of the most relevant publications.
7. Please note all documents or forms in which your invention has been recorded or described to substantiate your invention's history, such as lab notes. Whenever possible, it is desirable to have a witness sign such documents. Actual documents may be requested if patent application is filed.
10. Please list names and telephone numbers of individuals who possess technical or marketing knowledge related to your potential application that could assist in the commercial evaluation of the invention.
11. All inventors must sign and date the disclosure form. Only persons other than co-inventors who understand the invention may serve as witnesses; departmental colleagues are excellent resources.

**PLEASE SUBMIT ALL COPIES TO:** The University of Chicago  
Technology Center  
970 E. 58th Street  
Chicago, IL 60637

*Questions about the invention disclosure process, contact the Technology Center, Leonora Beck 702-8606.  
Questions about ARCH Development Corporation, contact Robert Nelson, 702-0304.*

2/90

HSV-1 (-) 839.5 + XR (3G)

Variables = time (virus → XR or XR → virus) & time (XR → subculture) 10

Overnight (ON) 24h P2A

time XR → virus -48 -24 -6 -3 -1  
time virus → XR +1 +3 +6 +24 +48

see the Tiggain

11

2

confluent plate =  $8 \times 10^6$  cells

Plate  $5 \times 10^4$ ,  $5 \times 10^5$ ,  $10^6$  for each time

Plate 100 200 300 for P5

	$5 \times 10^4$	$5 \times 10^5$	$10^6$	
<u>ON</u>				
-48	conf	conf	conf	
-24	conf	conf	conf	
-6				
-3	0			
-1	0	0	0	
+1			0	
+3				
+6	0	0		
+24	0	0	0	
+48	0	0	0	
P5	0	0	0	
<u>Oh</u>				
-48	conf	conf	conf	
-24?	conf	conf	conf	
-6	0	0	0	
-3			0	
-1			0	
+1	0	0	0	
+3	0	0	0	
+6	0	0	0	
+24	0	0	0	

HSV on for 6h per 3h

PE:  $5 \times 10^4$  0  $5 \times 10^5$  0  $10^6$  0

conf conf

10<sup>6</sup> - 25mL

2005mL 5.1mL 0.1mL

69

HSV-1 (-) 834.5 + XR (3 Cg)

Variables = Time (min → XR in sec → min) &amp; Time (22 → 24 → 26 → 28 → 30 → 32 → 34 → 36 → 38 → 40 → 42 → 44 → 46 → 48 → 50 → 52 → 54 → 56 → 58 → 60 → 62 → 64 → 66 → 68 → 70 → 72 → 74 → 76 → 78 → 80 → 82 → 84 → 86 → 88 → 90 → 92 → 94 → 96 → 98 → 100 → 102 → 104 → 106 → 108 → 110 → 112 → 114 → 116 → 118 → 120 → 122 → 124 → 126 → 128 → 130 → 132 → 134 → 136 → 138 → 140 → 142 → 144 → 146 → 148 → 150 → 152 → 154 → 156 → 158 → 160 → 162 → 164 → 166 → 168 → 170 → 172 → 174 → 176 → 178 → 180 → 182 → 184 → 186 → 188 → 190 → 192 → 194 → 196 → 198 → 200 → 202 → 204 → 206 → 208 → 210 → 212 → 214 → 216 → 218 → 220 → 222 → 224 → 226 → 228 → 230 → 232 → 234 → 236 → 238 → 240 → 242 → 244 → 246 → 248 → 250 → 252 → 254 → 256 → 258 → 260 → 262 → 264 → 266 → 268 → 270 → 272 → 274 → 276 → 278 → 280 → 282 → 284 → 286 → 288 → 290 → 292 → 294 → 296 → 298 → 300 → 302 → 304 → 306 → 308 → 310 → 312 → 314 → 316 → 318 → 320 → 322 → 324 → 326 → 328 → 330 → 332 → 334 → 336 → 338 → 340 → 342 → 344 → 346 → 348 → 350 → 352 → 354 → 356 → 358 → 360 → 362 → 364 → 366 → 368 → 370 → 372 → 374 → 376 → 378 → 380 → 382 → 384 → 386 → 388 → 390 → 392 → 394 → 396 → 398 → 400 → 402 → 404 → 406 → 408 → 410 → 412 → 414 → 416 → 418 → 420 → 422 → 424 → 426 → 428 → 430 → 432 → 434 → 436 → 438 → 440 → 442 → 444 → 446 → 448 → 450 → 452 → 454 → 456 → 458 → 460 → 462 → 464 → 466 → 468 → 470 → 472 → 474 → 476 → 478 → 480 → 482 → 484 → 486 → 488 → 490 → 492 → 494 → 496 → 498 → 500 → 502 → 504 → 506 → 508 → 510 → 512 → 514 → 516 → 518 → 520 → 522 → 524 → 526 → 528 → 530 → 532 → 534 → 536 → 538 → 540 → 542 → 544 → 546 → 548 → 550 → 552 → 554 → 556 → 558 → 560 → 562 → 564 → 566 → 568 → 570 → 572 → 574 → 576 → 578 → 580 → 582 → 584 → 586 → 588 → 590 → 592 → 594 → 596 → 598 → 600 → 602 → 604 → 606 → 608 → 610 → 612 → 614 → 616 → 618 → 620 → 622 → 624 → 626 → 628 → 630 → 632 → 634 → 636 → 638 → 640 → 642 → 644 → 646 → 648 → 650 → 652 → 654 → 656 → 658 → 660 → 662 → 664 → 666 → 668 → 670 → 672 → 674 → 676 → 678 → 680 → 682 → 684 → 686 → 688 → 690 → 692 → 694 → 696 → 698 → 700 → 702 → 704 → 706 → 708 → 710 → 712 → 714 → 716 → 718 → 720 → 722 → 724 → 726 → 728 → 730 → 732 → 734 → 736 → 738 → 740 → 742 → 744 → 746 → 748 → 750 → 752 → 754 → 756 → 758 → 760 → 762 → 764 → 766 → 768 → 770 → 772 → 774 → 776 → 778 → 780 → 782 → 784 → 786 → 788 → 790 → 792 → 794 → 796 → 798 → 800 → 802 → 804 → 806 → 808 → 810 → 812 → 814 → 816 → 818 → 820 → 822 → 824 → 826 → 828 → 830 → 832 → 834 → 836 → 838 → 840 → 842 → 844 → 846 → 848 → 850 → 852 → 854 → 856 → 858 → 860 → 862 → 864 → 866 → 868 → 870 → 872 → 874 → 876 → 878 → 880 → 882 → 884 → 886 → 888 → 890 → 892 → 894 → 896 → 898 → 900 → 902 → 904 → 906 → 908 → 910 → 912 → 914 → 916 → 918 → 920 → 922 → 924 → 926 → 928 → 930 → 932 → 934 → 936 → 938 → 940 → 942 → 944 → 946 → 948 → 950 → 952 → 954 → 956 → 958 → 960 → 962 → 964 → 966 → 968 → 970 → 972 → 974 → 976 → 978 → 980 → 982 → 984 → 986 → 988 → 990 → 992 → 994 → 996 → 998 → 1000

Overnight (Gib) 24h PCR

Time XR → min -48 -24 -6 -3 -1  
 min → XR +1 +3 +6 +24 +48

see the figure

Confluent plate =  $8 \times 10^6$  cellsPlate  $5 \times 10^4$ ,  $5 \times 10^5$ ,  $10^6$  for each time

Plate 100 200 300 for PB

	$5 \times 10^4$	$5 \times 10^5$	$10^6$
ON			
-48	conf	conf	conf
-24	conf	conf	conf
-6			
-3	0		
-1	0	0	0
+1			0
+3			0
+6	0	0	0
+24	0	0	0
+48	0	0	0
OK	0	0	0
Ohn			
-48	conf	conf	conf
-24	conf	conf	conf
-6	0	0	0
-3			
-1			
+1	0	0	0
+3	0	0	0
+6	0	0	0
+24	0	0	0
+48	0	0	0

HSV on for 6h per 73h

$5 \times 10^4$  R.  $5 \times 10^5$   $10^6$   
 conf conf conf

conf conf ~ 159/16

conf  $10^6$  + 25mL  
 $5 \times 10^4$   $5 \times 10^5$  L ~ 59/16  
 $5 \times 10^5$  - 1.2 mL

normal PB  $\frac{100}{500}$   $\frac{50}{100}$   $\frac{50}{300}$



				PFU again				75			

77

	Reproductive cell density	Test dependence of $K_2$	dependence of $K_2$ and $K_3$
	same dose: PE		
40	$1/200$	$\frac{52}{100}, \frac{106}{200}, \frac{108}{300}$	$10g$ $\frac{10}{500}, \frac{0}{10}, \frac{0}{10^4}$ $3Gg$ $\frac{27}{10}, \frac{0}{2 \times 10^3}, \frac{0}{10^5}$ $7Gg$ $\frac{0}{10}, \frac{0}{2 \times 10^4}, \frac{0}{10^5}$
4	$1/2000$	$\frac{36}{100}, \frac{94}{500}, \frac{167}{300}$	$\frac{137}{10}, \frac{0}{10^4}, \frac{172}{520}$ $\frac{0}{10^4}, \frac{5}{200}$ $\frac{200}{10^5}$ $\frac{0}{10^5}, \frac{40}{10^4}, \frac{0}{2 \times 10^4}$

Decant Medium

confluent SQ 200

infect  $\bar{c}$  40  $\mu$ l ( $1/200$ )

XRay 3Gg 6 hours after infect

Decant at 24°, 48°, feed

Noteshardly infected >  $1/200$  ( $1/10$ )

① SQ 200

② 10 h

③ PE at 10°, 10°

④ PE stain

⑤ infect with line on station 1 hr

→ ? could be due to toxicity

Test other cell types:

79

## Decanted CM

confluent x 4 days infected

1/200 NSV ± XR (36g) 6 hrs later

18 hr decant &amp; feed

80% on 202 of each onto confluent cells

## all 1/200 NSV

0 fed

0 fed → subculture

36g fed

36g fed → subculture

202 0 cm

202 0 cm → subculture 24°

202 36g

202 36g → subculture 24°

802 0

802 0 → mb 24°

802 36g

802 36g → mb 24°

24h CM 0 → ? mb 24°

24h CM 36g → ? mb 24°

48h CM 0

48h CM 36g

$$\frac{0}{100} \frac{122}{200} \frac{200}{500}$$

$$\frac{0}{500} \frac{152}{10} \frac{-800}{10^4}$$

$$\frac{0}{200} \frac{100}{500} \frac{226}{300}$$

$$\frac{0}{200} \frac{100}{500} \frac{300}{10} \frac{2000}{10}$$

$$\frac{61}{200} \frac{43}{100} \frac{162}{500}$$

$$\frac{153}{500} \frac{2100}{10^4} \frac{1000}{10^3}$$

$$\frac{0}{200} \frac{9}{500} \frac{0}{500}$$

$$\frac{0}{200} \frac{9}{500} \frac{0}{500}$$

$$\frac{0}{200} \frac{9}{500} \frac{0}{500}$$

cell gets offset?

↓  
P form on  
depletion or  
virus or  
infect (overgrown  
confluent)